Original Article

Childhood Cancer Mortality Trends in the Americas and Australasia: An Update to 2017

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BACKGROUND: Marked reductions in childhood cancer mortality occurred over the last decades in high-income countries and, to a lesser degree, in middle-income countries. This study aimed to monitor mortality trends in the Americas and Australasia, focusing on areas showing unsatisfactory trends. **METHODS:** Age-standardized mortality rates per 100,000 children (aged 0-14 years) from 1990 to 2017 (or the last available calendar year) were computed for all neoplasms and 8 leading childhood cancers in countries from the Americas and Australasia, using data from the World Health Organization database. A joinpoint regression was used to identify changes in slope of mortality trends for all neoplasms, leukemia, and neoplasms of the central nervous system (CNS) for major countries. **RESULTS:** Over the last decades, childhood cancer mortality continued to decrease by approximately 2% to 3% per year in Australasian countries (ie, Japan, Korea, and Australia), by approximately 1.5% to 2% in North America and Chile, and 1% in Argentina. Other Latin American countries did not show any substantial decrease. Leukemia mortality declined in most countries, whereas less favorable trends were registered for CNS neoplasms, particularly in Latin America. Around 2016, death rates from all neoplasms were 4 to 6 per 100,000 boys and 3 to 4 per 100,000 girls in Latin America, and 2 to 3 per 100,000 boys and approximately 2 per 100,000 girls in North America and Australasia. **CONCLUSIONS:** Childhood cancer mortality trends declined steadily in North America and Australasia, whereas they were less favorable in most Latin American countries. Priority must be given to closing the gap by providing high-quality care for all children with cancer worldwide. ***Cancer* 2021;127:3445-3456**.

LAY SUMMARY:

- Advances in childhood cancer management have substantially improved the burden of these neoplasms over the past 40 years, particularly in high-income countries.
- This study aimed to monitor recent trends in America and Australasia using mortality data from the World Health Organization.
- Trends in childhood cancer mortality continued to decline in high-income countries by approximately 2% to 3% per year in Japan, Korea, and Australia, and 1% to 2% in North America.
- Only a few Latin American countries showed favorable trends, including Argentina, Chile, and Mexico, whereas other countries with limited resources still lagged behind.

KEYWORDS: America, Asia, cancer, childhood, mortality, Oceania, trends.

INTRODUCTION

Cancer is among the top 10 leading causes of death among children worldwide.[1,2] Over 200,000 new cases and 70,000 cancer deaths at age 0 to 14 years were estimated in 2018 worldwide. Of these, over 80% occurred in low- and middle-income countries, where specialized pediatric centers are located in major cities only, resources are limited, and standards of care cannot be guaranteed.[2-7] Restricted access to care for children living in rural areas often results in delayed diagnosis, high toxicity, and treatment discontinuation with unfavorable effects that undermine the achievement of the high-survival rates observed in high-income countries.[3,8-10]

Despite the advances in early diagnosis and treatment of pediatric cancers, substantial differences in mortality between high-income and low-/middle-income countries persist.[8,11-14] Childhood cancer mortality trends showed

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Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33642, **Received:** November 16, 2020; **Revised:** March 19, 2021; **Accepted:** April 26, 2021, **Published online** May 27, 2021 in Wiley Online Library (wileyonlinelibrary.com)

steady declines from 1970 to 2007 in selected countries from North America and Australasia, whereas patterns were less favorable in most Latin American countries, with rates of approximately 5 per 100,000 boys and 4 per 100,000 girls aged 0 to 14 years in 2005-2007, comparable to those registered in high-income countries in the early 1980s.[14]

To monitor recent trends in childhood cancer mortality in those areas, we updated the analysis of mortality up to 2017 based on the World Health Organization (WHO) database.

MATERIALS AND METHODS

From the WHO mortality database, we extracted the numbers of deaths at 0 to 14 years of age from all neoplasms malignant and benign combined (codes of the 10th Revision of the *International Classification of Diseases* [*ICD-10*]: C00-D48) in selected countries from the Americas and Australasia from 1990 up to 2017 (or the last available year).[15] We also considered cancers of the liver (*ICD 10* code: C22), bone and articular cartilage (*ICD 10* codes: C40-C41), connective and soft tissue (*ICD 10* codes: C47, C49), kidney and other urinary sites (*ICD 10* codes: C64-C66, C68), eye (*ICD 10* code: C69), neoplasms of the central nervous system (CNS; including benign, malignant, and those of uncertain or unknown behavior of brain and CNS; *ICD 10* codes: C70-C72, C75.1-C75.3, D32-D33, D43), non-Hodgkin lymphoma (NHL; *ICD 10* codes: C82-C85, C86, C88, C96), and leukemia (*ICD 10* codes: C91-C95), also including acute lymphoblastic leukemia (ALL; *ICD 10* code: C91.0) and acute myeloblastic leukemia (AML; *ICD 10* code: C92.0) separately. When a different revision of the *ICD* was used, we recoded the causes of death for each country and calendar year according to the *ICD-10*.[16] For neoplasms of the CNS, we only used data registered according to the *ICD-10* because it had a new and expanded coding system.[17]

We also extracted estimates of the resident populations from the same WHO database based on official censuses for countries from Australasia.[15] For the American countries, we retrieved population data from the Pan American Health Organization.[18]

We analyzed the data for 18 countries (12 from the Americas and 6 from Australasia), selected according to population size (over 500,000 inhabitants aged 0-14 years) and estimated mortality coverage of at least 85% (most of them greater equal 90%).

For each cause, country, sex, and calendar year, we derived age-specific rates for 4 age groups (<1, 1-4, 5-9, 10-14 years), and then computed the age-standardized mortality rates per 100,000 children based on the world standard population, and the 95% confidence intervals (CI) for the overall rates.[19]

For a subset of 12 selected countries with over 2 million population aged 0-14 years, with an adequate number of deaths during the studied period (ie, annual average deaths in 2015-2017 over 50), we performed a joinpoint regression analysis[20] on mortality trends for all neoplasms combined and the 2 most common cancers at these ages: leukemia and neoplasms of the CNS. We thus identified the time point(s) called joinpoint(s), when a change in the linear slope (on a log scale) of the temporal trend occurred, by testing from zero up to a maximum of 3 joinpoints. As a summary measure, we estimated the annual percent change (APC) for each identified linear segment and the weighted average APC (AAPC) over the entire studied period (1990-2017).[21,22]

RESULTS

Table 1 shows the age-standardized mortality rates (at age 0-14 years) from all childhood neoplasms, leukemia, and neoplasms of the CNS per 100,000 children (overall and stratified by sex) in 20 selected countries from the Americas and Australasia, in the triennia 2005-2007 and 2015-2017, the average yearly deaths of the latest period, and the corresponding percent change in rates. Figure 1 shows bar plots with rates of the latest period ordered from the highest to the lowest for boys, girls, and both sexes combined (with 95% CIs for the overall rates).

Overall rates were highest in Latin American countries, in particular Cuba, Mexico, and Colombia (over 4.5 per 100,000) and lowest in North America, Oceania, and Israel (below 2.5 per 100,000).

Among boys, mortality rates from all neoplasms declined from 2005-2007 to 2015-2017 in most countries considered, except Colombia, Costa Rica, Cuba, Australia, and New Zealand. The highest mortality rates in 2005-2007 were registered in Colombia, Cuba, Mexico, and Venezuela (rates over 5 per 100,000), whereas the lowest ones were in Australia (2.5 per 100,000), Canada, the United States, and Japan (2.8 per 100,000). Similarly, in 2015-2017, the highest rates were observed in Latin American countries, reaching rates over 5 per 100,000 in Colombia (5.4), Cuba (5.9), and Mexico (5.2), whereas the lowest ones were reported in Japan (2.2), Israel, the Republic of Korea (both 2.4), Australia (2.5), and North America (2.5 in the United States and 2.6 in Canada). Among girls, all neoplasms mortality rates declined during the decade considered in most countries, except in Chile, Costa Rica, and Panama. Mortality rates

TABLE 1. Age-Standardized (World Population) Mortality Rates at Age 0-14 Years per 100,000 Children From All Neoplasms, Leukemia, and Neoplasms of the CNS in Selected Countries From the Americas and Australasia in 2005-2007 and 2015-2017 and the Annual Average Deaths of the Latest Period and the Corresponding % Change[a] in Rates

	Boys				Girls				Boys and Girls			
	ASMR 2005-2007	ASMR 2015-2017	Annual Average Deaths	% Change	ASMR 2005-2007	ASMR 2015-2017	Annual Average Deaths	% Change	ASMR 2005-2007	ASMR 2015-2017	Annual Average Deaths	% Change
All neoplasms												
Canada	2.80	2.62	77	−6.4	2.44	2.14	61	−12.3	2.62	2.38	69	−9.2
United States	2.79	2.50	776	−10.4	2.50	2.22	658	−11.2	2.64	2.37	717	−10.2
Argentina	4.90	4.23	237	−13.7	3.86	3.72	199	−3.6	4.39	3.98	218	−9.3
Brazil	4.60	4.33	1036	−5.9	3.87	3.74	849	−3.4	4.24	4.04	943	−4.7
Chile	4.26	3.55	66	−16.7	2.97	3.40	59	14.5	3.62	3.48	63	−3.9
Colombia	5.33	5.39	320	1.1	4.64	4.32	246	−6.9	4.99	4.87	283	−2.4
Costa Rica	4.72	4.95	27	4.9	3.61	3.62	19	0.3	4.18	4.30	23	2.9
Cuba	5.48	5.85	55	6.8	4.19	3.96	34	−5.5	4.85	4.93	45	1.6
Guatemala	4.51	4.12	126	−8.6	3.86	3.32	98	−14.0	4.19	3.73	112	−11.0
Mexico	5.67	5.20	929	−8.3	4.91	4.62	788	−5.9	5.30	4.92	859	−7.2
Panama	4.67	4.27	24	−8.6	3.91	4.60	24	17.6	4.29	4.43	24	3.3
Puerto Rico	1.77	1.26	5	—	1.81	1.78	6	—	1.79	1.52	5	—
Uruguay	3.78	2.78	10	−26.5	2.54	2.61	9	—	3.17	2.70	10	−14.8
Venezuela[b]	5.48	5.70	251	4.0	4.52	4.90	205	8.4	5.01	5.30	228	5.8
Hong Kong SAR	3.87	3.33	15	−14.0	2.54	2.22	9	—	3.22	2.79	12	−13.4
Israel	3.02	2.37	30	−21.5	2.43	2.27	27	−6.6	2.73	2.32	28	−15.0
Japan	2.80	2.19	175	−21.8	2.28	1.92	145	−15.8	2.55	2.06	160	−19.2
Republic of Korea	3.97	2.44	86	−38.5	3.52	1.96	65	−44.3	3.76	2.21	76	−41.2
Australia	2.46	2.51	59	2.0	2.49	1.91	43	−23.3	2.47	2.22	51	−10.1
New Zealand	3.09	3.45	16	11.7	3.20	2.21	9	—	3.14	2.84	13	−9.6
Leukemia												
Canada	0.59	0.56	16	−5.1	0.54	0.43	12	−20.4	0.57	0.50	14	−12.3
United States	0.78	0.61	187	−21.8	0.61	0.51	149	−16.4	0.69	0.56	168	−18.8
Argentina	1.71	1.61	90	−5.8	1.34	1.26	68	−6.0	1.53	1.44	79	−5.9
Brazil	1.47	1.50	363	2.0	1.19	1.20	275	0.8	1.33	1.35	319	1.5
Chile	1.56	1.43	27	−8.3	1.11	1.01	18	−9.0	1.34	1.22	23	−9.0
Colombia	2.39	2.23	135	−6.7	1.90	1.71	99	−10.0	2.15	1.98	117	−7.9
Costa Rica	1.28	2.04	11	59.4	1.68	1.53	8	—	1.47	1.79	10	21.8
Cuba	1.79	1.75	16	−2.2	1.23	1.28	12	4.1	1.52	1.52	14	0.0
Guatemala	1.88	2.05	63	9.0	1.74	1.32	39	−24.1	1.81	1.69	51	−6.6
Mexico	2.54	2.34	425	−7.9	2.18	2.07	359	−5.0	2.36	2.21	392	−6.4
Panama	1.50	1.86	10	24.0	1.38	2.05	11	48.6	1.44	1.95	11	35.4
Puerto Rico	0.57	0.17	1	—	0.52	0.24	1	—	0.55	0.21	1	—
Uruguay	0.86	0.75	3	—	0.43	0.66	2	—	0.65	0.70	2	—
Venezuela[b]	2.04	2.13	94	4.4	1.69	1.80	76	6.5	1.87	1.97	85	5.3

TABLE 1. *Continued*

	Boys				Girls				Boys and Girls			
	ASMR 2005-2007	ASMR 2015-2017	Annual Average Deaths	% Change	ASMR 2005-2007	ASMR 2015-2017	Annual Average Deaths	% Change	ASMR 2005-2007	ASMR 2015-2017	Annual Average Deaths	% Change
Hong Kong SAR	1.31	0.61	3	—	0.66	0.59	2	—	1.00	0.60	3	—
Israel	0.75	0.29	4	—	0.61	0.60	7	—	0.69	0.44	5	—
Japan	0.81	0.54	43	−33.3	0.62	0.48	37	−22.6	0.72	0.51	40	−29.2
Republic of Korea	1.55	0.83	29	−46.5	1.28	0.57	19	−55.5	1.42	0.70	24	−50.7
Australia	0.44	0.58	14	31.8	0.53	0.44	10	−17.0	0.48	0.51	12	6.3
New Zealand	0.89	0.88	4	—	0.92	0.54	2	—	0.90	0.71	3	—
Neoplasms of central nervous system												
Canada	1.08	1.15	34	6.5	0.90	0.89	26	−1.1	0.99	1.03	30	4.0
United States	0.91	0.89	283	−2.2	0.90	0.81	242	−10.0	0.91	0.85	263	−6.6
Argentina	1.38	1.25	70	−9.4	1.17	0.96	51	−17.9	1.28	1.11	61	−13.3
Brazil	1.19	1.16	276	−2.5	1.10	1.09	246	−0.9	1.15	1.13	261	−1.7
Chile	1.05	1.07	19	1.9	0.81	1.15	20	42.0	0.93	1.11	20	19.4
Colombia	1.10	1.42	84	29.1	0.91	1.22	69	34.1	1.01	1.32	76	30.7
Costa Rica	1.23	1.28	7	—	0.81	0.89	5	—	1.02	1.09	6	—
Cuba	1.45	1.73	17	19.3	1.00	0.96	8	—	1.23	1.36	13	10.6
Guatemala	0.65	0.55	17	−15.4	0.51	0.79	23	54.9	0.58	0.67	20	15.5
Mexico	1.09	1.14	203	4.6	0.98	1.05	178	7.1	1.03	1.10	191	6.8
Panama	1.19	0.97	5	—	0.84	0.59	3	—	1.02	0.78	4	—
Puerto Rico	0.30	0.30	1	—	0.34	1.13	4	—	0.32	0.70	2	—
Uruguay	1.22	0.71	3	—	0.83	0.74	3	—	1.03	0.72	3	—
Venezuela[b]	1.22	1.37	61	12.3	1.08	1.13	48	4.6	1.15	1.25	54	8.7
Hong Kong SAR	1.20	0.84	4	—	1.21	0.66	3	—	1.21	0.75	3	—
Israel	1.33	1.04	13	−21.8	0.76	0.73	9	—	1.05	0.89	11	−15.2
Japan	0.85	0.85	69	0.0	0.77	0.75	58	−2.6	0.81	0.80	63	−1.2
Republic of Korea	0.92	0.67	24	−27.2	0.92	0.75	25	−18.5	0.92	0.71	25	−22.8
Australia	0.97	1.10	26	13.4	0.99	0.77	17	−22.2	0.98	0.94	22	−4.1
New Zealand	1.07	0.64	3	—	1.06	0.47	2	—	1.07	0.55	3	—

Abbreviations: ASMR, Age-standardized mortality rate; CNS, central nervous system.

[a]When the annual average deaths were <10, the % change was not shown.

[b]For Venezuela, since data were not available from 2015-2017, the rate and the annual average deaths data refers to 2012-2014.

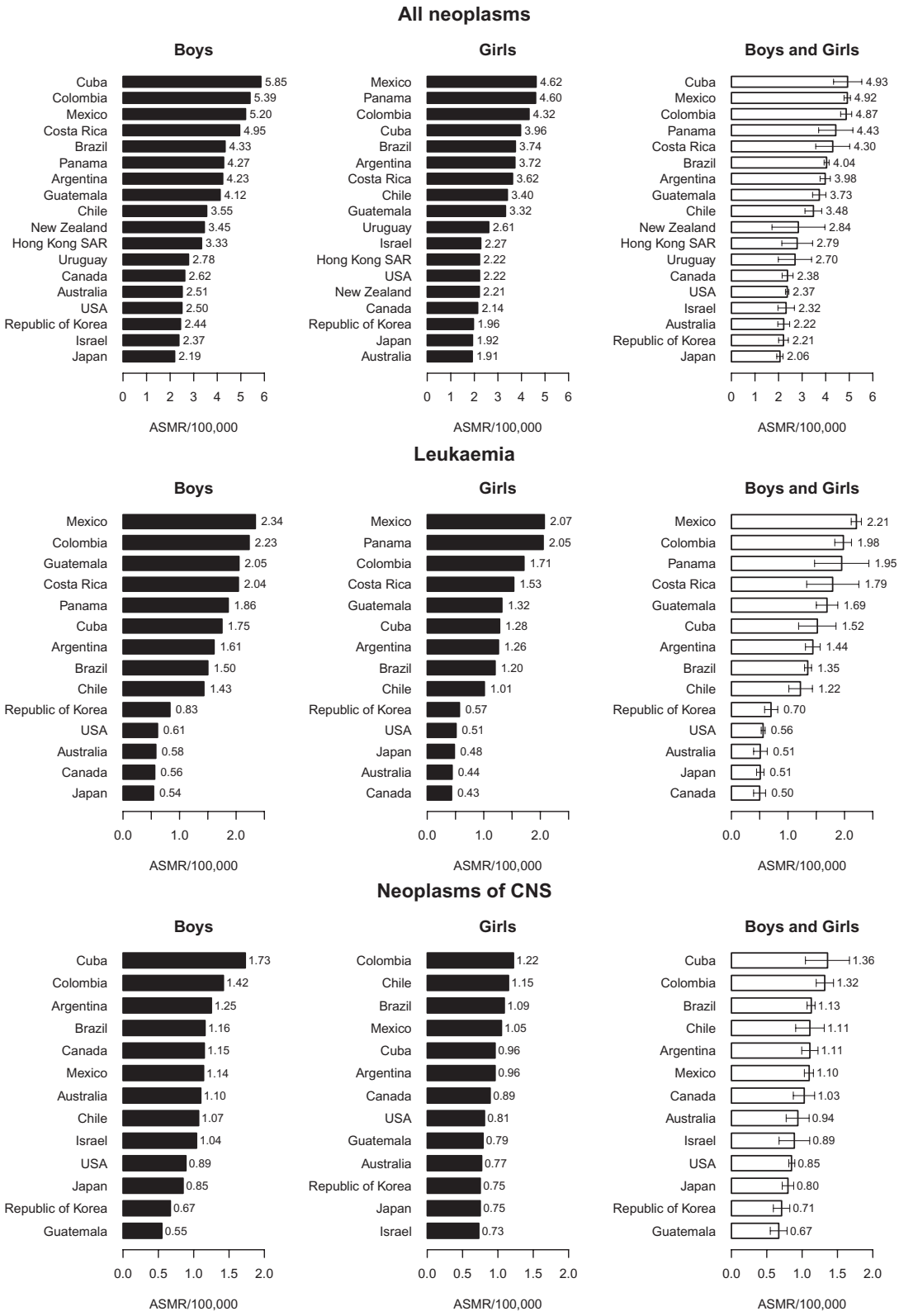

Figure 1. Bar plots of age-standardized (world population) mortality rates (ASMRs) per 100,000 children (aged 0-14 years) from all neoplasms, leukemia, and neoplasms of the central nervous system (CNS) in boys and girls separately and combined, ordered from the highest to the lowest rate around 2016 (2015-2017).

in 2005-2007 ranged between over 2.0 and almost 5.0 per 100,000, with the highest rates in Colombia (4.6), Cuba (4.2), Mexico (4.9), and Venezuela (4.5), and the lowest ones between 2.3 to 2.5 per 100,000, in Canada, the United States, Uruguay, Hong Kong, Israel, Japan, and Australia. In 2015-2017, the highest rates were reported in Colombia (4.3), Mexico, and Panama (4.6 per 100,000), whereas the lowest ones in countries from North America and Australasia, with rates approximately 2 per 100,000 girls.

Leukemia mortality rates in boys decreased during the studied decades in most countries with some exceptions, including Brazil, Costa Rica, Guatemala, Panama, and Australia. In 2005-2007, the rates ranged from 0.4 in Australia, followed by Canada, the United States, and Japan (0.6-0.8 per 100,000) to 2.5 per 100,000 in Mexico, followed by Colombia (2.4 per 100,000) and Venezuela (2.0 per 100,000). Similar figures emerged during the most recent period considered, with the highest rates in Colombia, Costa Rica, Guatemala, and Mexico (2.0-2.3 per 100,000) and the lowest ones in Canada, the United States, Japan, and Australia (0.5-0.6 per 100,000). In girls, leukemia mortality rates decreased in most countries, except in Brazil, Cuba, and Panama. Rates in 2005-2007 varied between 0.5-0.6 per 100,000 in North America, Israel, Japan, and Australia and 2.2 per 100,000 in Mexico. The highest mortality rates in 2015-2017 were registered in Mexico and Panama (2.1 per 100,000), whereas the lowest mortality rates in North America and most Australasian regions were 0.4-0.6 per 100,000 girls.

Mortality rates from CNS neoplasms among boys decreased in some countries, including the United States, Argentina, Brazil, Guatemala, Israel, and the Republic of Korea, but not in others. Over the decade considered, the highest death rates were reported in Cuba (1.5 per 100,000 in 2005-2007 and 1.7 per 100,000 in 2015-2017), whereas the lowest were in Guatemala and the Republic of Korea (0.65-0.9/100,000 in 2005-2007 and 0.6-0.7/100,000 in 2015-2017), as well as in Japan (0.85/100,000 in both calendar periods). In girls, mortality rates from neoplasms of the CNS decreased in most countries, with the exceptions of Chile, Colombia, Guatemala, and Mexico. In 2005-2007, rates ranged from 0.5 per 100,000 in Guatemala, 0.8 per 100,000 in Japan, 0.9 per 100,000 in Canada and the United States, 1 per 100,000 in Mexico and Australia, to 1.2 per 100,000 in Argentina and Hong Kong. During the most recent period, the highest rates were registered in Chile and Colombia (~1.2/100,000) and the lowest ones in countries from Australasia (0.5-0.8/100,000), as well as in Guatemala.

Figure 2 shows the trends in age-standardized mortality rates (dots) and corresponding joinpoint models (lines) for all neoplasms for 12 major countries from the Americas and Australasia over the 1990-2017 period. Corresponding trends for leukemia and neoplasms of the CNS are shown in Figure 3. The estimates of the APCs and AAPCs obtained from the joinpoint analysis are reported in Table 2.

Total childhood cancer mortality showed favorable trends in both sexes, except in Brazil, Colombia, and Mexico, where the trend was stable or rising slightly. Rates in Mexican boys decreased since the early 2000s (APC: −0.7% since 2001). The most favorable patterns were in the Republic of Korea (APC: −3.5% in both sexes), Australia (APC: −2.8% in boys and −2.5% in girls) and Japan (APC: −2.6% in boys and −2.2% in girls), but also in North America, where rates dropped annually by 1.8% in boys and 1.6% in girls in Canada, and by approximately 1.8% and 1.4%, respectively, in the United States. A favorable pattern also emerged in Chile (APC: −1.9% in boys and −.6% in girls) and in Cuban girls (APC: −1.3%) though rates were too sparse.

Childhood leukemia mortality showed favorable trends in both sexes and most countries considered, except in Brazilian and Colombian boys, where the trends were stable over time. Rates in Mexico increased until 2000 (APC: +1.8% in boys and +1.5% in girls) and declined thereafter (APC: −0.9% in boys and −0.7% in girls since 2000). The most favorable patterns were in North American and Australasian countries. The greatest declines were reported in Australia (by 5.1% per year in boys and 4.9% per year in girls), followed by Japan and the Republic of Korea (APCs: −4.1% and −4.5%, in boys, respectively, and −3.9% and −4.3% in girls), as well as in Canada and the United States (APCs: −3.5% and −3% in boys, respectively, and −2.8% and −2.4% in girls).

Trends in CNS neoplasms mortality were less clear. However, favorable patterns were observed in some countries, including the United States, Chile (in boys), Japan, and the Republic of Korea, with the greatest AAPCs approximately −3% in Korea in both sexes. Stable or less-favorable trends emerged in the other countries, particularly in Colombia and Mexico.

Supporting Table 1 gives the age-standardized mortality rates from the other less common childhood cancers: liver, bone and cartilage, connective and soft tissue, kidney

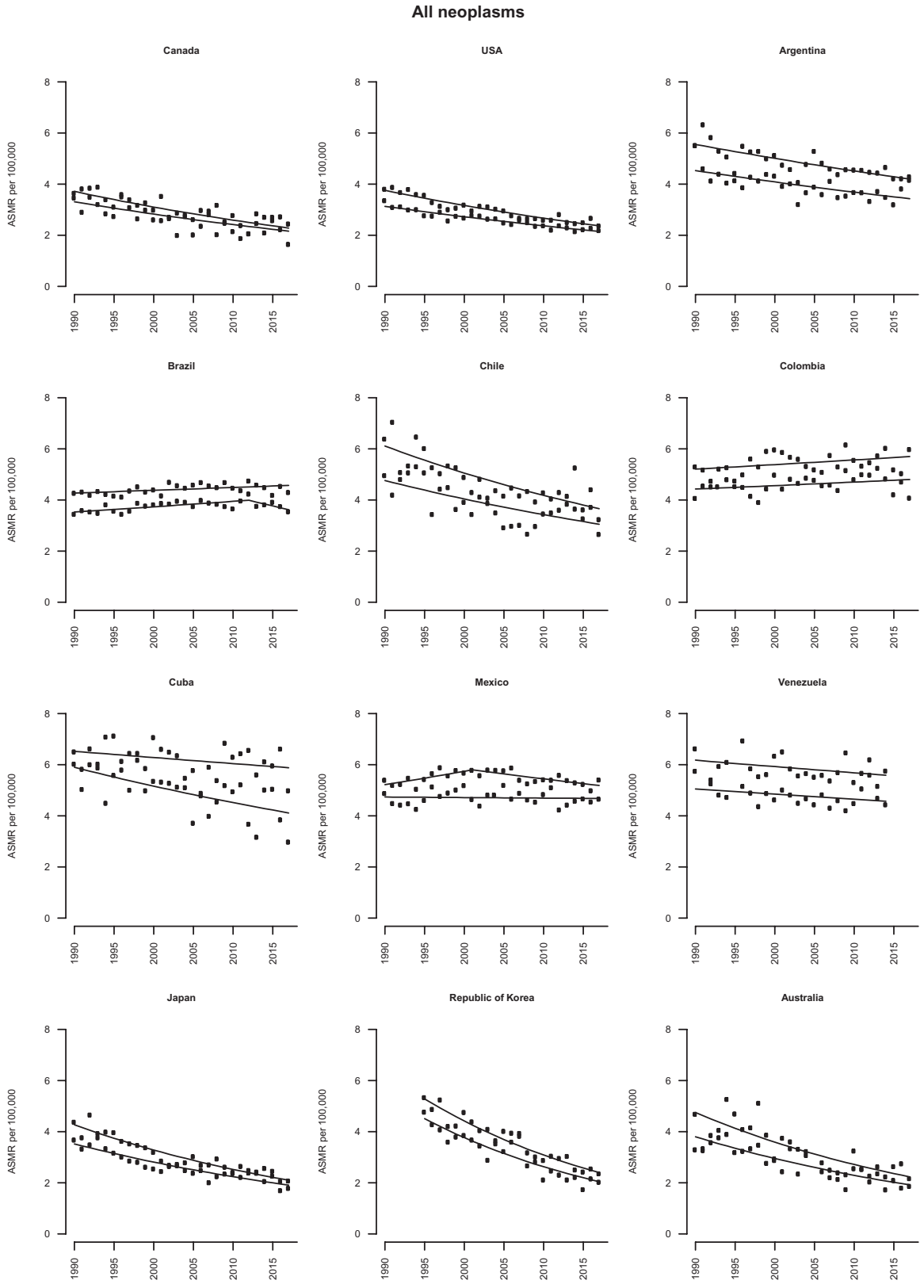

Figure 2. Trends in age-standardized mortality rates (ASMRs; dots: full for boys and empty for girls) and corresponding joinpoint models (lines) for all neoplasms for 12 major countries from the Americas and Australasia over the period 1990-2017 according to data availability.

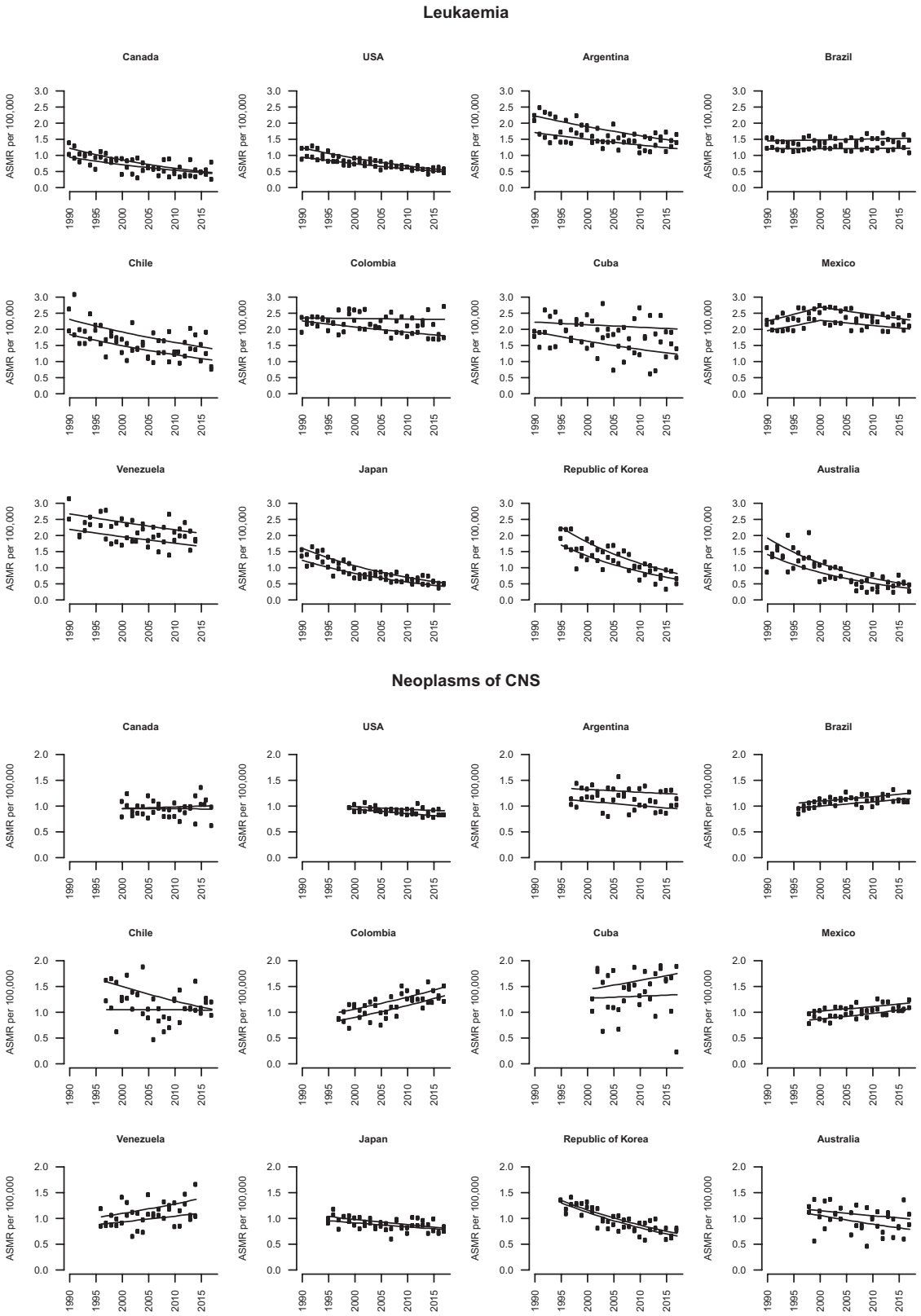

Figure 3. Trends in age-standardized mortality rates (ASMRs; dots: full for boys and empty for girls) and corresponding joinpoint models (lines) for leukemia and neoplasms of the central nervous system (CNS) for 12 major selected countries over the period 1990-2017 according to data availability.

TABLE 2. Joinpoint analysis for all neoplasms, leukemia, and neoplasms of the CNS from 1990 to 2017 (according to data availability) by country and sex

	Boys					Girls				
	Trend 1	APC 1	Trend 2	APC 2	AAPC	Trend 1	APC 1	Trend 2	APC 2	AAPC
All neoplasms										
Canada	1990-2017	−1.8*			−1.8*	1990-2017	−1.6*			−1.6*
United States	1990-1998	−2.7*	1998-2017	−1.4*	−1.8*	1990-2017	−1.4*			−1.4*
Argentina	1990-2017	−1*			−1*	1990-2017	−1*			−1*
Brazil	1990-2017	0.2*			0.2*	1990-2012	0.6*	2012-2017	−1.9	0.1
Chile	1990-2017	−1.9*			−1.9*	1990-2017	−1.6*			−1.6*
Colombia	1990-2017	0.3*			0.3*	1990-2017	0.3			0.3
Cuba	1990-2017	−0.4			−0.4	1990-2017	−1.3*			−1.3*
Mexico	1990-2001	1*	2001-2017	−0.7*	0	1990-2017	0			0
Venezuela	1990-2014	−0.4			−0.4	1990-2014	−0.4			−0.4
Japan	1990-2017	−2.6*			−2.6*	1990-2017	−2.2*			−2.2*
Republic of Korea	1995-2017	−3.5*			−3.5*	1995-2017	−3.5*			−3.5*
Australia	1990-2017	−2.8*			−2.8*	1990-2017	−2.5*			−2.5*
Leukemia										
Canada	1990-2017	−3.5*			−3.5*	1990-2017	−2.8*			−2.8*
United States	1990-2017	−3*			−3*	1990-2017	−2.4*			−2.4*
Argentina	1990-2017	−1.6*			−1.6*	1990-2017	−1.3*			−1.3*
Brazil	1990-2017	0.2			0.2	1990-2017	0			0
Chile	1990-2017	−1.8*			−1.8*	1990-2017	−2.1*			−2.1*
Colombia	1990-2017	−0.1			−0.1	1990-2017	−0.8*			−0.8*
Cuba	1990-2017	−0.4			−0.4	1990-2017	−1.7*			−1.7*
Mexico	1990-2000	1.8*	2000-2017	−0.9*	0.1	1990-2000	1.5*	2000-2017	−0.7*	0.1
Venezuela	1990-2014	−1*			−1*	1990-2014	−1.1*			−1.1*
Japan	1990-2017	−4.1*			−4.1*	1990-2017	−3.9*			−3.9*
Republic of Korea	1995-2017	−4.5*			−4.5*	1995-2017	−4.3*			−4.3*
Australia	1990-2017	−5.1*			−5.1*	1990-2017	−4.9*			−4.9*
Neoplasms of the CNS										
Canada	2000-2017	0.3			0.3	2000-2017	0			0
United States	1999-2017	−0.5			−0.5	1999-2017	−1*			−1*
Argentina	1997-2017	−0.4			−0.4	1997-2017	−0.8			−0.8
Brazil	1996-2017	0.8*			0.8*	1996-2017	0.8*			0.8*
Chile	1997-2017	−2*			−2*	1997-2017	0			0
Colombia	1997-2017	2*			2*	1997-2017	2.3*			2.3*
Cuba	2001-2017	1.2			1.2	2001-2017	0.3			0.3
Mexico	1998-2017	0.9*			0.9*	1998-2017	1.2*			1.2*
Venezuela	1996-2014	1.6			1.6	1996-2014	1.1			1.1
Japan	1995-2017	−1.1*			−1.1*	1995-2017	−0.9*			−0.9*
Republic of Korea	1995-2017	−2.9*			−2.9*	1995-2017	−3.1*			−3.1*
Australia	1998-2017	−0.8			−0.8	1998-2017	−1.7			−1.7

Abbreviations: AAPC, average annual percent change; APC, annual percent change; CNS, central nervous system.
*Significantly different from 0 ($p < 0.05$).

and other urinary organs, eye, NHL, ALL, and AML in selected countries from American and Australasian areas in the calendar periods 2005-2007 and 2015-2017, and the annual average deaths of the latest period.

DISCUSSION

Childhood cancer mortality trends continued to be favorable during the last 2 to 3 decades in high-income countries, with declines by approximately 2% to 3% per year in Japan, Korea, and Australia, and 1% to 2% in North America and Chile as well. A downward trend was also observed in Argentina and a slight improvement emerged among Mexican boys since 2001, whereas no substantial changes were found in the other Latin American countries. Deaths from leukemia and CNS neoplasms accounted for over 60% of all cancer deaths in children. The declining trend in total cancer mortality was mostly driven by a marked decline in leukemia mortality. In North America, the declines in rates from leukemia were driven by ALL, whereas in Latin America the recorded declines were driven by AML (Supporting Table 1). This may be because of the increasing fraction of induction deaths in acute leukemia in developing countries, which require well-equipped centers with better supportive cancer care guidelines.[23]

However, some degree of misclassification is possible, as well as issues of random variation caused by a low number of deaths. Less favorable trends were registered for neoplasms of the CNS, particularly in Latin America.[24] In the United States, Canada, Japan, and Australia, death rates from neoplasms of the CNS were higher than those from leukemia, reflecting the lack of substantial improvements in the treatment of these malignancies, even in high-income countries.[24] In contrast, leukemia remained the main cause of childhood cancer deaths in Latin American countries—likely as a consequence of delays in diagnosis and lack of access to advanced treatments, as well as treatment discontinuation.[3,8,25] Moreover, children with cancer from several Latin American countries must often be referred to universal health care systems in places far from their place of residence.[25]

Childhood cancer mortality rates in countries from North America and Australasia are comparable or even more favorable to those registered in Western Europe, whereas most Latin American countries still showed rates higher than those of Central-Eastern European countries, the area with the highest rates in Europe.[12]

The encouraging trends in childhood cancer mortality observed during the last decades in the countries included in this analysis are largely based on important advancements in effective therapies. Childhood cancer survival estimates vary broadly among countries worldwide. Globally, survival estimates showed a 70% gap between high- and low-income countries, with the best 5-year–net survival being over 80% in North America, comparable with several, but not all European countries.[24,26,27] In most of Latin America, pediatric cancer registers are still in the development stage, and for some countries reliable survival estimates are difficult to obtain.[28]

The countries included in this study have different health care systems, and childhood cancer mortality and survival are important indicators of the quality and equity of the national health care system.[29,30] The socioeconomic context and the widespread inequalities in low- and middle-income countries do not allow for the provision of all citizens with adequate care; a low socioeconomic status can limit access to accurate diagnosis and effective treatment.[6,31] This is particularly true for leukemia, which requires up-to-date and long-term treatments that families in a low socioeconomic context cannot afford.[32] In fact, higher mortality was reported among children born in a lower socioeconomic status, both in high- and low-/middle-income countries.[31,33-36]

Most childhood cancer trends in Latin American countries were not encouraging, however there were a few exceptions. Among these, the most favorable pattern emerged in Chile, and has been largely related to an efficient pediatric-oncology care program implemented recently.[30,37] Survival in that country approximates that of the United States.[24,37] Despite the economic difficulties that Argentina has faced over the last 2 decades and the following cutbacks in public expenditures, recent mortality data are promising, although the absolute values remain comparably high.[38] The increasing attention toward pediatric oncology, as reflected by a well-organized national population-based registry implemented in the late 1990s, has likely been contributing to the improved management of childhood cancers.[28,39] Mexico presented in the past increasing mortality trend(s) from childhood cancers, which started to decline since the early 2000s. This is, in large part, the result of changes in medical health care after the health care reform in 2003 and the Popular Medical Insurance launched in 2005, aimed to develop a national standardized program of multidisciplinary care, particularly for childhood cancers.[13,40] The unfavorable trends in Brazil could be explained by an improvement in diagnostic ability and certification, as shown by the remarkable decrease in mortality caused by ill-defined causes observed since the mid-1990s (Supporting Fig. 1).

Mortality rates depend on both incidence and survival, but the observed heterogeneity across different areas of the world is more likely caused by low survival. In most Latin American countries, in fact, the incidence of leukemia and CNS tumors is similar or slightly lower, possibly due to differences in registration in those countries as opposed to North America and Australasia, where survival is substantially higher. Incidence can be influenced by changes in diagnostic ability and registration, and the scarcity of cancer registries in low- and middle-income countries may result in the underreporting of new cases.[6,13,40] Mortality data can be affected by variability in coding and death certification across calendar periods and countries. However, our data were based on official national official sources, and we restricted our analysis to countries with satisfactory death-certification coverage and a meaningful numbers of cases to improve validity and consistency across the countries considered. Underreporting could have somewhat affected the estimates for some countries. For example, it could be a reason of the lowest mortality rate from CNS tumors observed in Guatemala. However, we do not have evidence to confirm this hypothesis.

Our up-to-date analysis of childhood cancer mortality confirms the persisting improvement of outcomes

in pediatric oncology in high-income countries based on important advances in management and treatment. These same mortality reductions should also be achievable in middle-and low-income countries, including most of Latin America.

FUNDING SUPPORT

This work was supported by the Italian Foundation for Cancer Research (project no. 22987) and the Ministero dell'Istruzione, dell'Università e della Ricerca with a Scientific Independence of Young Researchers 2014 grant (project no. RBSI1465UH).

CONFLICT OF INTEREST DISCLOSURES

All authors have declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Matteo Malvezzi: Conceptualization, methodology, and writing–review and editing. **Claudia Santucci:** Formal analysis, and writing–original draft. **Gianfranco Alicandro:** Methodology, and writing–review and editing. **Greta Carioli:** Data curation, methodology, and writing–review and editing. **Paolo Boffetta:** Conceptualization, and writing–review and editing. **Karina Braga Ribeiro:** Writing–review and editing; **Fabio Levi:** Conceptualization, and writing–review and editing; **Carlo La Vecchia:** Conceptualization, and writing–review and editing. **Eva Negri:** Conceptualization, and writing–review and editing; **Paola Bertuccio:** Conceptualization, supervision, data curation, methodology, and writing–original draft.

REFERENCES

1. Bhakta N, Force LM, Allemani C, et al. Childhood cancer burden: a review of global estimates. *Lancet Oncol*. 2019;20:e42-e53.
2. Collaborators GBDCC. The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. *Lancet Oncol*. 2019;20:1211-1225.
3. Denburg A, Cuadrado C, Alexis C, et al. Improving childhood cancer care in Latin America and the Caribbean: a PAHO Childhood Cancer Working Group position statement. *Lancet Oncol*. 2017;18:709-711.
4. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer. Accessed October 15, 2019. https://gco.iarc.fr/today
5. Gupta S, Rivera-Luna R, Ribeiro RC, Howard SC. Pediatric oncology as the next global child health priority: the need for national childhood cancer strategies in low- and middle-income countries. *PLoS Med*. 2014;11:e1001656.
6. Magrath I, Steliarova-Foucher E, Epelman S, et al. Paediatric cancer in low-income and middle-income countries. *Lancet Oncol*. 2013;14:e104-e116.
7. Basbous M, Al-Jadiry M, Belgaumi A, et al. Childhood cancer care in the Middle East, North Africa, and West/Central Asia: a snapshot across five countries from the POEM network. *Cancer Epidemiol*. 2021;71(Pt B):101727.
8. Curado MP, Pontes T, Guerra-Yi ME, Cancela Mde C. Leukemia mortality trends among children, adolescents, and young adults in Latin America. *Rev Panam Salud Publica*. 2011;29:96-102.
9. Friedrich P, Lam CG, Kaur G, Itriago E, Ribeiro RC, Arora RS. Determinants of treatment abandonment in childhood cancer: results from a global survey. *PLoS One*. 2016;11:e0163090.
10. Howard SC, Zaidi A, Cao X, et al. The My Child Matters programme: effect of public-private partnerships on paediatric cancer care in low-income and middle-income countries. *Lancet Oncol*. 2018;19:e252-e266.
11. American Cancer Society. Cancer Facts & Figures 2020. American Cancer Society; 2020.
12. Bertuccio P, Alicandro G, Malvezzi M, et al. Childhood cancer mortality trends in Europe, 1990-2017, with focus on geographic differences. *Cancer Epidemiol*. 2020;67:101768.
13. Rivera-Luna R, Zapata-Tarres M, Shalkow-Klincovstein J, et al. The burden of childhood cancer in Mexico: Implications for low- and middle-income countries. *Pediatr Blood Cancer*. 2017;64:e26366.
14. Chatenoud L, Bertuccio P, Bosetti C, Levi F, Negri E, La Vecchia C. Childhood cancer mortality in America, Asia, and Oceania, 1970 through 2007. *Cancer*. 2010;116:5063-5074.
15. World Health Organization Statistical Information System. WHO Mortality Database. Accessed July 20, 2020. http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html
16. World Health Organization. International Statistical Classification of Disease and Related Health Problems: 10th Revision. World Health Organization; 1992.
17. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer*. 2005;103:1457-1467.
18. Pan American Health Organization (PAHO). Health Information Platform for the Americas. Accessed July 20, 2020. http://www.paho.org/data/index.php/en/indicators/demographics-core/308-poblacion-nac-en.html
19. Doll R, Smith PG, Waterhouse JAH, et al. Comparison between registries: age-standardized rates. Vol. IV. IARC Sci Publ No. 42. Cancer Incidence in Five Continents, 1982:671-675.
20. National Cancer Institute. Joinpoint Regression Program, version 4.1. Accessed 20 July, 2020. http://srab.cancer.gov/joinpoint/
21. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. *Stat Med*. 2009;28:3670-3682.
22. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. (Erratum in: *Stat Med*. 2001;20:655). *Stat Med*. 2000;19:335-351.
23. Hafez HA, Soliaman RM, Bilal D, Hashem M, Shalaby LM. Early deaths in pediatric acute leukemia: a major challenge in developing countries. *J Pediatr Hematol Oncol*. 2019;41:261-266.
24. Siegel DA, Richardson LC, Henley SJ, et al. Pediatric cancer mortality and survival in the United States, 2001-2016. *Cancer*. 2020;126:4379-4389.
25. Guzman CP, Cordoba MA, Godoy N, et al. Childhood cancer in Latin America: from detection to palliative care and survivorship. *Cancer Epidemiol*. 2021;71(Pt B):101837.
26. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Girardi F, Atun R. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. *Lancet Oncol*. 2019;20:972-983.
27. Bonaventure A, Harewood R, Stiller CA, et al. Worldwide comparison of survival from childhood leukaemia for 1995-2009, by subtype, age, and sex (CONCORD-2): a population-based study of individual data for 89 828 children from 198 registries in 53 countries. *Lancet Haematol*. 2017;4:e202-e217.
28. Fedorovsky JM, Cuervo LG, Luciani S. Pediatric cancer registries in Latin America: the case of Argentina's pediatric cancer registry. *Rev Panam Salud Publica*. 2017;41:e152.
29. La Vecchia C, Levi F, Lucchini F, Lagiou P, Trichopoulos D, Negri E. Trends in childhood cancer mortality as indicators of the quality of medical care in the developed world. *Cancer*. 1998;83:2223-2227.
30. Ribeiro RC, Steliarova-Foucher E, Magrath I, et al. Baseline status of paediatric oncology care in ten low-income or mid-income countries receiving My Child Matters support: a descriptive study. *Lancet Oncol*. 2008;9:721-729.
31. Houweling TA, Kunst AE. Socio-economic inequalities in childhood mortality in low- and middle-income countries: a review of the international evidence. *Br Med Bull*. 2010;93:7-26.
32. Winestone LE, Aplenc R. Disparities in survival and health outcomes in childhood leukemia. *Curr Hematol Malig Rep*. 2019;14:179-186.
33. Jabeen K, Ashraf MS, Iftikhar S, Belgaumi AF. The impact of socioeconomic factors on the outcome of childhood acute lymphoblastic leukemia (ALL) treatment in a low/middle income country (LMIC). *J Pediatr Hematol Oncol*. 2016;38:587-596.
34. Kehm RD, Spector LG, Poynter JN, Vock DM, Altekruse SF, Osypuk TL. Does socioeconomic status account for racial and ethnic disparities in childhood cancer survival? *Cancer*. 2018;124:4090-4097.

35. Johnson KJ. Disparities in pediatric and adolescent cancer survival: a need for sustained commitment. *Cancer*. 2020;126:4273-4277.
36. Alicandro G, Bertuccio P, Sebastiani G, La Vecchia C, Frova L. Parental education and cancer mortality in children, adolescents, and young adults: a case-cohort study within the 2011 Italian census cohort. *Cancer*. 2020;126:4753-4760.
37. Palma J, Mosso C, Paris C, et al. Establishment of a pediatric HSCT program in a public hospital in Chile. *Pediatr Blood Cancer*. 2006;46:803-810.
38. Moreno F, Loria D, Abriata G, Terracini B, network R. Childhood cancer: incidence and early deaths in Argentina, 2000-2008. *Eur J Cancer*. 2013;49:465-473.
39. Moreno F, Dussel V, Orellana L, network R. Childhood cancer in Argentina: survival 2000-2007. *Cancer Epidemiol*. 2015;39:505-510.
40. Abdullaev FI, Rivera-Luna R, Roitenburd-Belacortu V, Espinosa-Aguirre J. Pattern of childhood cancer mortality in Mexico. *Arch Med Res*. 2000;31:526-531.